

REMARKS

A. Regarding the Amendments

By the present communication claims 116 and 164 have been amended to more particularly define Applicants' invention. As amended, the claims are supported by the specification and the original claims and add no new matter. For example, support for the phrase "through the vessel wall" as recited in claims 116 and 164 is found in the specification at 33, lines 17-19 and page 70 lines 26 and 27. In addition, support for the ultrasonic frequency range of "750 kHz to 3 MHz" is found in the specification at page 69, line 4. It is submitted that the amendments place the claims in condition for allowance, or in better condition for appeal. Accordingly, entry of the amendments is respectfully requested. Claims 116-184 are pending.

B. Priority

In a prior Office Action mailed July 20, 2001 (Paper No. 19), the Examiner asserted that the effective priority date for the present invention is October 6, 1999, the filing date of the present application, since the parent case (now issued U.S. Patent No. 6,033,645) allegedly does not teach methods for enhancing bioavailability of bioactive agents. Applicant respectfully disagrees with this assertion. The '645 patent teaches methods for enhancing bioavailability of bioactive agents throughout, and specifically at col. 5, lines 28-29, and lines 56-61; and at col. 7, lines 37-49. Thus, it is respectfully submitted that the basis for not allowing the priority claim is unclear. Accordingly, since the parent case teaches methods for enhancing bioavailability of bioactive agents, Applicant respectfully requests that the present application be granted an effective priority date of June 19, 1996.

C. Double Patenting Rejections

Claims 116-131, 138-141, 146-151, 160, 164, 168-174, and 178-185 stand rejected under the judicially created doctrine of obviousness-type double patenting in view of U.S. Patent Nos. 6,443,898, 6,416,740, and 6,403,056. While Applicant respectfully traverses this rejection, it is believed that this issue is addressed by the terminal disclaimers which accompany this response. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 116-131, 138-141, 146-151, 160, 164, 168-174, and 178-185 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over the pending claims of copending Application Nos. 09/075,477, 09/218,660, 09/813,484, and 10/055,772. Should rejection over the copending applications be maintained, Applicant reserves the right to address such rejections once claims are allowed in those applications.

D. Rejections Under 35 U.S.C. § 102

The rejection of claims 116-131, 138-140, 160, 164-166, 168-174, and 178-184 under 35 U.S.C. § 102(b) as allegedly being anticipated by Siegel et al. (U.S. Patent No. 5,695,460), is respectfully traversed. Applicant's invention, as defined, for example, by claim 116, distinguishes over Siegel et al. by requiring a method for enhancing the delivery of a bioactive agent from the vasculature to a selected tissue in a patient, comprising:

- (i) administering said bioactive agent to said patient;
- (ii) administering a vesicle composition to said patient, by intravascular infusion, wherein said vesicle composition comprises, in an aqueous carrier, vesicles comprising lipids, proteins, or polymers and a gas or gaseous precursor; and
- (iii) applying ultrasonic energy to the patient in an amount sufficient to produce cavitation or rupture of said vesicles, and sufficient to increase delivery of said bioactive agent

from the vasculature through the vessel wall and into said selected tissue, wherein said bioactive agent is delivered into said selected tissue.

Siegel et al. neither expressly nor inherently sets forth each and every element of the invention as defined for example, in claim 116. In particular, Siegel et al. does not describe applying ultrasonic energy in an amount sufficient to increase delivery of a bioactive agent from the vasculature through the vessel wall and into selected tissue. Indeed, those skilled in the art recognize that the low ultrasound frequencies described in Siegel et al. (i.e., 85, 105, and 243 kHz) are insufficient to deliver a bioactive agent from the vasculature through the vessel wall and into selected tissue.

Moreover, it is respectfully submitted that Siegel et al. does not describe either expressly or inherently administration by intravascular infusion. Instead Siegel et al. requires that the vesicle composition be introduced proximate to the area of need in a patient (see, e.g., col. 2, line 12). This is in contrast to the present invention, which does not require proximate placement of the vesicle composition in order to achieve efficient delivery to the area of need.

Applicant's invention, as defined by claim 164, further distinguishes over Siegel et al. by requiring a method for enhancing the delivery of a bioactive agent from the vasculature to a selected tissue in a patient, comprising:

- (i) administering said bioactive agent to said patient;
- (ii) administering an acoustically active composition to said patient, by intravascular infusion; and
- (iii) applying ultrasonic energy to the patient in an amount sufficient to activate said acoustically active composition, and sufficient to increase delivery of said bioactive agent from the vasculature and into said selected tissue, wherein said bioactive agent is delivered into said selected tissue and said ultrasound energy has a frequency of from about 750 kHz to 3 MHz.

It is respectfully submitted that Siegel et al. does not describe such a method. In particular, the ultrasonic frequency range recited in present claim 164 is clearly outside the range contemplated by Siegel et al. Indeed, Siegel et al. teaches away from the presently claimed frequency range by reciting frequencies of 85, 105, and 243 kHz, and by reciting that lower frequencies (i.e., 25-39 kHz) are optimal (see col. 5, lines 29-38 and col. 7, lines 45-56). Further, it is known in the art that lower frequencies in ultrasound have higher energy so Siegel et al. actually teaches away from Applicant's use of higher frequencies, which have lower energy and which are so highly effective in the claimed methods of the invention.

For all of the reasons set forth above, it is respectfully submitted that Siegel et al. does not describe each and every element of the claimed invention. Accordingly, reconsideration and withdrawal of the rejection of claims 116-131, 138-140, 160, 164-166, 168-174, and 178-184 under 35 U.S.C. § 102(b) are respectfully requested.

The rejection of claims 116-131, 138-141, 146-151, 160, 164, 168-174, and 178-185 under 35 U.S.C. § 102 (e) as allegedly being anticipated by Klaveness et al. (U.S. Patent No. 6,331,289), and Schneider is respectfully traversed. Applicant respectfully submits that, for the reasons cited in Part B of this response, the present application is entitled to an effective filing date of June 19, 1996, thereby antedating Klaveness et al., and Schneider et al.

E. Rejections Under 35 U.S.C. § 103(a)

The rejection of claims 141, 146-151, and 185 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Siegel et al., is respectfully traversed. It is respectfully submitted that Siegel et al. does not suggest the methods of the present invention.

Applicant has discovered that administering a gaseous composition or acoustically active composition to a patient by continuous infusion enhances delivery of a bioactive agent from the vasculature through the vessel wall and into selected tissue of a patient. The present

claims recite that the acoustically active composition be administered to a patient by continuous infusion and that ultrasonic energy be applied in an amount sufficient to deliver a bioactive agent from the vasculature through the vessel wall and into selected tissue. In contrast, Siegel et al. requires that an echo contrast agent containing microbubbles be delivered to the vasculature of a patient, and that the contrast agent must be delivered proximate to the area of need in the patient. Siegel et al. also describes the use of low frequency ultrasonic energy relative to the ultrasonic frequency range set forth in the present invention. Clearly, there is no suggestion in Siegel et al. that a bioactive agent could be administered by continuous infusion (i.e., not proximate to tissue in need of said agent). There is also no suggestion in Siegel et al. that a bioactive agent could be delivered from the vasculature through the vessel wall and into selected tissue. Finally, Siegel et al. clearly does not suggest the frequency range set forth in the present invention (i.e., 750 kHz to about 3 MHz), and instead teaches away from the present invention by stating that low frequencies are optimal for the methods described therein.

For all of the reasons set forth above, it is respectfully submitted that the rejection of claims 141, 146-151, and 185 under 35 U.S.C. § 103(a) is not properly applied. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

The rejection of claims 116-131, 138-141, 146-151, 160, 164-166, 168-174, and 178-184 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Porter (U.S. Patent No. 5,648,098) in view of Siegel et al. is respectfully traversed.

As set forth above, Siegel et. al. discloses methods of delivering a contrast agent to a blood vessel in order to dissolve arterial thrombi. Like Siegel et al. Porter is directed to thrombolytic therapy. Also like Siegel et al. Porter does disclose or suggest delivery of bioactive agent from the vasculature through the vessel wall and into selected tissue. In addition, there is no suggestion in Porter to use the ultrasonic frequency range set forth in the

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Application No.: 09/413,110
Filed: October 6, 1999
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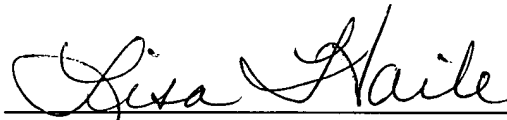
presently claimed methods. Thus, neither Porter nor Siegel et al. alone or in combination, disclose or suggest the methods of the present invention. Accordingly, reconsideration and withdrawal of the rejection of claims 116-131, 138-141, 146-151, 160, 164-166, 168-174, and 178-184 under 35 U.S.C. § 103(a) are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: March 4, 2004



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